REVIEW

Micronutrients impact the gut microbiota and blood glucose

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This paper is part of a collection of articles exploring Gut Microbiome and Endocrinology, across the Journal of Endocrinology and the Journal of Molecular Endocrinology.

Abstract

Micronutrients influence hormone action and host metabolism. Dietary minerals, trace elements, and vitamins can alter blood glucose and cellular glucose metabolism, and several micronutrients are associated with the risk and progression of type 2 diabetes. Dietary components, microbes, and host immune, endocrine, and metabolic responses all interact in the intestine. There has been a focus on macronutrients modifying the host-microbe relationship in metabolic disease. Micronutrients are positioned to alter host-microbe symbiosis that participates in host endocrine control of glucose metabolism. Minerals and trace elements can alter the composition of the intestinal microbiota, gut barrier function, compartmentalized metabolic inflammation, cellular glucose transport, and endocrine control of glucose metabolism, including insulin and thyroid hormones. Dietary vitamins also influence the composition of the intestinal microbiota and vitamins can be biotransformed by gut microbes. Host-microbe regulation of vitamins can alter immunity, lipid and glucose metabolism, and cell fate and function of pancreatic beta cells. Causal effects of micronutrients in host-microbe metabolism are still emerging, and the mechanisms linking dietary excess or deficiency of specific micronutrients to changes in gut microbes directly linked to metabolic disease risk are not yet clear. Dietary fiber, fat, protein, and carbohydrates are key dietary factors that impact how microbes participate in host glucose metabolism. It is possible that micronutrient and microbiota-derived factors also participate in host-microbe responses that tip the balance in the endocrine control of host glucose metabolism. Dietary micronutrients should be considered, tested, and controlled in pre-clinical and clinical studies investigating host-microbe factors in metabolic diseases.

Key Words

- ▶ intestinal
- ▶ microbiome
- ▶ nutrition
- ▶ diabetes
- ▶ lipid
- ▶ insulin
- ▶ resistance
- ▶ glucose

Journal of Endocrinology
(2021) **250**, R1–R21

Introduction

There is interest in understanding the impact of composition and function of intestinal-resident bacterial communities (i.e. the gut microbiota) on host metabolism. A major challenge is ascribing function to bacterial communities, strains, and metabolites

and how each influences aspects of host metabolism. In addition, determining directionality in the host-microbe relationship that leads to actionable outcomes in metabolic disease is an important challenge. It is critical to determine the environmental factors and host

characteristics that influence host-microbe relationships in metabolic health and disease. Many factors shape the microbial ecosystems residing within different intestinal and tissue compartments, and bacteria or bacterial components that penetrate host extra-intestinal tissues (Gérard 2016, Anhê *et al.* 2020a). The intestine harbors the majority of commensal microbes in humans. Nutrients, bacteria, and host cells that direct immune, endocrine, and metabolic responses directly interact within the intestinal environment (Thursby & Juge 2017). Given that diet is a key factor in metabolic diseases, it is important to understand how dietary components interact and alter the connections between microbes and host immunity and metabolism. It is known and well-characterized that macronutrients and fiber can alter the composition of the intestinal microbiota. In this review, we will summarize how micronutrients can influence the community composition and possibly the function of the microbiota, which relay signals that impact host metabolism and metabolic disease like obesity. Uncovering the complex relationship between diet, gut bacteria, and host metabolism may reveal aspects of how obesity worsens blood glucose control. This review focuses on how micronutrients influence host glucose metabolism by altering the host-microbe relationship.

Gut microbes and metabolic disease

Modifying the composition of the gut microbiota can impact metabolism. For example, low-dose antibiotic administration during a critical window of development can increase body mass, which persists later in life in livestock and mice (Cox *et al.* 2014). Sub-therapeutic antibiotic treatment in the early life of mice altered gut microbial composition, increased microbial metabolites such as short-chain fatty acid (SCFA) levels in the colon, increased adipose tissue mass, and changed hepatic gene expression related to carbohydrate and lipid metabolism (Cho *et al.* 2012).

Studies using rodents that are born with no bacteria have revealed some of the bacterial contributions to host metabolism. Germ-free mice extract less energy from food, demonstrating that bacteria regulate intestinal energy extraction. Microbial influence on digestion and intestinal absorption of dietary components and energy content is a key mechanism by which bacteria influence energy balance (Bäckhed *et al.* 2004). Metabolic disease states, like obesity, can alter the gut microbiota to promote more energy extraction from food (Bäckhed *et al.* 2007).

The gut microbiota can also influence blood glucose. Lower bacterial diversity correlates with insulin resistance and higher adiposity (reviewed in Zhu & Goodarzi 2020). Type 2 diabetes (T2D) is associated with an altered composition of the gut microbiota, where the lower relative abundance of Firmicutes *Clostridia*, but higher *Betaproteobacteria* in diabetic humans was associated with higher blood glucose. There are many correlations between taxonomy and possible host functions. For example, the Firmicutes phylum consists predominantly of SCFA butyrate-producing bacteria; specifically, certain *Clostridia* have anti-inflammatory properties and are less abundant in individuals with T2D. *Faecalibacterium prausnitzii* is another butyrate-producing strain that is associated with improvements in glucose tolerance in patients who have undergone gastric bypass surgery, suggesting that bacterial metabolites can also affect glucose homeostasis. In addition, branched-chain amino acids produced by *Bacteroides vulgatus* species positively correlate with insulin resistance (Pedersen *et al.* 2016, Zhu & Goodarzi 2020). Lastly, the commonly prescribed glucose-lowering agent metformin in T2D can alter gut microbes by increasing SCFA-producing bacteria and mucin-degrading *Akkermansia muciniphila* while increasing intestinal glucose absorption and glucagon-like peptide-1 production (McCreight *et al.* 2016, Vallianou *et al.* 2019). Although there are fewer examples of microbes or microbial communities causing changes in blood glucose, the microbiota from obese mice can transmit higher blood glucose into germ-free mice independently of changes in adiposity (Foley *et al.* 2018).

Overall, this supports the concept that the microbiota participates in host blood glucose control. Diet is a major factor in shaping the composition and function of the gut microbiota. The effects of dietary fiber and macronutrients on the gut microbiota are rapid and reproducible (David *et al.* 2014). The purpose of this review is to highlight the state of knowledge for micronutrients altering the host-microbe relationship relevant to host glucose metabolism.

Macronutrients and gut microbes

Diet composition continuously shapes the gut microbiota, in a bidirectional relationship between bacterial composition/function and dietary components (Rinninella *et al.* 2019). Although the human gut microbiota is largely dominated by two key phyla, Firmicutes and Bacteroidetes, shifts in the relative abundance of these and less abundant phyla due to altered diet can impact host immunity and metabolism (Rinninella *et al.* 2019).

Macronutrients including fats, carbohydrates, and proteins provide most of the energy content of food, and each is processed to varying degrees by both host and gut microbes.

Fats are the most energy-dense macronutrient and an efficient means to store energy. Excess intake of dietary fat alters the composition of the intestinal microbiota disrupting host-microbe equilibrium (i.e. dysbiosis), fueling pro-inflammatory responses in the host, and, therefore, contributes to obesity and insulin resistance (Cândido *et al.* 2018, Bisanz *et al.* 2019). The importance of dietary fat on the composition of gut microbiota and consequences for metabolic disease are well-reviewed (Shen *et al.* 2014).

Carbohydrates are another important dietary macronutrient that are particularly important in altering blood glucose. Carbohydrates can be generally classified into digestible and indigestible. The former is easily processed by the host for energy, whereas the latter can be processed by gut bacteria (Chassard & Lacroix 2013). The topic of carbohydrates and gut microbiota is also well-described (Chassard & Lacroix 2013). Dietary fiber is a subcategory of fermentable and non-fermentable indigestible carbohydrates that has a major impact on the composition and function of the gut microbiota (Dalby *et al.* 2017, Makki *et al.* 2018).

Dietary protein content influences the composition of the gut microbiota and simultaneously, gut bacteria can help biotransform dietary protein. Sources of protein (i.e. animal vs plant), the amino acid composition of proteins, and consumed quantities can all affect bacterial amino acid metabolism and metabolite production. In addition, recent evidence demonstrated that modifying protein from casein to a bacterial-derived source of protein during feeding of a high fat and high sugar diet can reverse western diet-induced gut bacterial changes and improve insulin sensitivity (Jensen *et al.* 2021). The plethora of variables involved in protein metabolism can have significant consequences for host health and disease and have been reviewed elsewhere (Zhao *et al.* 2019).

Micronutrients: minerals, trace elements, gut microbes, and glucose metabolism

Dietary intake of trace minerals and vitamins are required in smaller amounts compared to macronutrients (generally in the milligram range), but its intake is critical for the regulation of many physiological processes, including metabolism. In general, trace minerals, also referred to as trace elements, make up less than 0.01% of the total body weight or are required in amounts between

1 and 100 mg/day in adults (Mehri 2020). Vitamins are organic compounds that are water or fat-soluble and can be essential micronutrients (Lykstad & Sharma 2020). A summary outlining the effects of trace elements on gut bacteria and host metabolism is provided in Tables 1, 2 and 3.

Chromium

Chromium exists either in the most stable oxidation trivalent (3+) state found in food or the strongly oxidizing hexavalent (6+) state generated from industrial pollution. Inorganic chromium exists in the soil. Plants secrete organic acids that can act as carrier molecules, therefore increasing the solubility and promoting the uptake and conversion of inorganic chromium into its organic form (Sharma *et al.* 2020). Food sources of chromium include meats, whole grains, fruits, vegetables, and spices (National Institutes of Health 2020a). Chromium supplementation in individuals with T2D is associated with improved blood glucose control (Paiva *et al.* 2015). Supplementing high fat-fed mice with chromium reduced body weight, lowered hepatic and circulating triglycerides, and improved insulin sensitivity by increasing hepatic insulin signaling (Chen *et al.* 2010). In addition, chromium restriction *in utero* promotes glucose intolerance, hyperglycemia, hyperinsulinemia, and insulin resistance in adult murine offspring (Zhang *et al.* 2016). Finally, a recent meta-analysis showed that chromium supplementation lowers fasting plasma glucose, hemoglobin A1c, and triglyceride levels while increasing circulating high-density lipoprotein (HDL) cholesterol in type 2 diabetic patients (Huang *et al.* 2018). Altogether, these results demonstrate an association of chromium with blood glucose.

The link between chromium and the gut microbiota is starting to emerge. Chromium supplementation using a probiotic strain (*Bacillus subtilis*) in mice promoted insulin secretion and lowered blood glucose, which was associated with higher skeletal muscle insulin receptor levels, and an improved circulating lipid profile (Yang *et al.* 2016). Although inorganic chromium caused some of these metabolic effects, supplementation with probiotic-produced organic chromium had greater metabolic outcomes (Yang *et al.* 2016). Therefore, the bioavailability and/or biological activity of chromium is an important determinant for its metabolic effects, with the gut microbiota positioned to relay these divergent metabolic effects. Organic and inorganic forms of chromium have different effects on intestinal flora. Compared to inorganic chromium, organic chromium supplementation increased

Table 1 The effects of non-metal trace elements on the gut microbiome and host metabolism.

Trace element	Recommended dietary allowance (RDA)	Effects on gut microbiome	Effect on metabolism
Fluoride (F)	Male: 4 mg [^] Female: 3 mg [^] Pregnant: 3 mg [^] Lactation: 3 mg [^]	F supplementation in broiler chickens ↑ <i>Escherichia coli</i> , <i>Enterococcus</i> spp. ↓ <i>Lactobacillus</i> spp., <i>Bifidobacterium</i> spp., diversity F exposure Laying hens: ↓SCFAs, intestinal barrier, ↑Enteric pathogens; Proteobacteria, Acidobacteria, Chloroflexi, Actinobacteria; Alphaproteobacteria, Betaproteobacteria, Ktedonobacteria Mice: ↓Firmicutes ↑Bacteroidetes, Actinobacteria ↓crypt depth, epithelial cell proliferation, goblet cells, glycoproteins, and mast cells in cecal tissue	F supplementation: ↑insulin sensitivity, hepatic GLUT 4 ↓Hepatic PEPCK, gluconeogenesis ↓APO-E → ↓cholesterol biosynthesis (LDL and total cholesterol High F doses: Hyperinsulinemia, IR, glucose intolerance (in rats with renal deficiency (1–15 ppm)), impaired insulin signaling
Iodine (I)	Male: 150 µg Female: 150 µg Pregnant: 220 µg Lactation: 290 µg	HF-fed I-supplemented vs HF-control mice: ↑Bacterial species of <i>Enterococcus</i> , <i>Clostridium</i> , and <i>Fusobacterium</i> <i>nucleatum</i> ↑enteric pathogenic bacteria ↓ <i>Faecalibacterium prausnitzii</i> , <i>Lactobacillus</i> , and <i>Bifidobacterium</i> Supplementation, independent of fat ↑ <i>Oscillibacter</i> , <i>Allobaculum</i> : ↓ <i>Blautia</i>	Deficient and excess status linked to T2DM Supplementation: ↓BW, adiposity, liver weight ↑blood thyroid hormone (TSH, TT3, FT3, FT4) High I dose: Pancreatic destruction, hyperglycemia Impair beta cell insulin secretion, apoptosis
Selenium (Se)	Male: 55 µg Female: 55 µg Pregnant: 60 µg Lactation: 70 µg	Decreased Se associated with IBD Se supplementation in broiler chickens: ↓Enteric pathogens; mitigates Ochratoxin-induced ↓α-diversity, oxidative stress, inflammation	Deficient and excess status linked to IR, T2DM; hepatokine selenoprotein P linked to IR Se Supplementation in CHF and diabetic CHD ↓serum insulin, HOMA-IR, LDL, CRP ↑HDL, insulin sensitivity, antioxidant levels; ↓Beta cell oxidative damage and H2O2 induced insulin signaling.

RDA values based on adults aged 19–50 years old.

[^]Adequate intake (AI) values are given for F.

ALT, alanine transaminase; APO-E, apolipoprotein E; AST, aspartate aminotransferase; BW, body weight; CHF, congestive heart failure; CHD, coronary heart disease; FBG, fasting blood glucose; FT3, free triiodothyronine (T3); FT4, free thyroxine (T4); HDL, high density lipoprotein; HbA1c, hemoglobin A1c; HF, high fat; HTN, hypertension; IBD, inflammatory bowel disease; IR, insulin resistance; Kdo, keto-deoxyoctulosonate; LDL, low density lipoprotein; LPS, lipopolysaccharide; NAFLD, non-alcoholic fatty liver disease; PTEN, phosphatase and tensin homolog protein; RIP3, receptor-interacting protein kinase 3; s.c., subcutaneously; SCFA, short chain fatty acids; T2M, type 2 diabetes; TAG, triacylglycerol; TSH, thyroid-stimulating hormone; TT3, total triiodothyronine (T3); wks, weeks.

the number of gram-positive bacteria in type 2 diabetic rats, which correlated with improved insulin sensitivity and circulating cardiovascular measures (Feng *et al.* 2015) (Fig. 1). The carrier molecule is also a critical characteristic contributing to diverging metabolic effects since rats administered chromium malate had increased gram-positive bacteria and decreased gram-negative bacteria compared to administration of chromium picolinate (Feng *et al.* 2015). Microbial changes correlating with chromium malate coincided with lower fasting blood glucose, circulating triglycerides, and total/LDL cholesterol (Feng *et al.* 2015) (Fig. 1). The metabolic effects of organic chromium malate were greater than any other chromium source tested in a type 2 diabetic rat model, suggesting that the type of chromium and its relationship with the gut

microbiota should be considered regarding the metabolic impact of this micronutrient. Overall, these results demonstrate the effects of chromium on the gut microbiota and host metabolism are dependent on the organic vs inorganic source of this trace element and the compound it is attached to, which may influence its bioavailability, therefore impacting the host-microbe relationship.

Copper

Copper is involved in many enzymatic and oxidation-reduction reactions. Dietary sources of copper include nuts, shellfish, whole-grain products, mushrooms, and tofu (National Institutes of Health 2019). Higher circulating copper levels are associated with impaired blood glucose

Table 2 The effects of transition metal trace elements on the gut microbiome and host metabolism.

Trace element	Recommended dietary allowance (RDA)	Effects on gut microbiome	Effect on metabolism
Chromium (Cr)	Male: 35 µg [^] Female: 25 µg [^] Pregnant: 30 µg [^] Lactation: 45 µg [^]	Probiotic <i>B. subtilis</i> Cr in mice ↑Cecal <i>Lactobacillus</i> , <i>Bifidobacterium</i> ↓ <i>Escherichia coli</i> , <i>Staphylococcus</i> Organic vs Inorganic Cr supplementation in rats Organic Cr improved insulin sensitivity, ↑Fecal Gram positive bacteria vs inorganic Cr ↑Fecal Gram positive bacteria, ↓ Gram negative cocci in Cr Malate vs Cr Picolinate	Probiotic <i>B. subtilis</i> Cr in mice ↑HDL, Insulin ↓LDL, total cholesterol, TAGs, Glucose Cr supplementation HF-fed mice: ↓BW, hepatic TAGs, IR Diabetics: ↓FBG, HbA1c, TAGs; ↑HDL Cr restriction (<i>In utero</i>) Glucose intolerance, hyperinsulinemia, IR
Copper (Cu)	Male: 900 µg Female: 900 µg Pregnant: 1.3 mg Lactation: 1.3 mg	Increased Cu associated with IBD Different Cu sources on gut microbiota Rats: Cu-Chitosan Nanoparticle ↓ <i>Salmonella</i> , <i>Clostridium</i> ↑ <i>Lactobacilli</i> SCFAs vs Cu sulfate Rats: Probiotic Cu delivery ↑ <i>Lachnospiraceae</i> , <i>Ruminococcaceae</i> , <i>Intestinibacter</i> High Cu exposure Pigs: ↓ <i>Clostridia</i> , <i>Roseburia</i> , <i>Acidaminococcus</i> , <i>Coprococcus</i> ; ↑ <i>Fibrobacteres</i> Carp: ↓ <i>Lactobacillus</i> , <i>Bacillus</i> , and <i>Akkermansia</i> ; ↑Pathogens, ↓growth indices, tight junction	High circulating levels correlates to T2DM Copper bound to ceruloplasmin positively correlates with IR, BMI, T2DM risk High Cu diets→ enhanced hepatic lipid/TAG content, lipogenic genes Marginal Cu diets + fructose → NAFLD development
Manganese (Mn)	Male: 2.3 mg [^] Female: 1.8 mg [^] Pregnant: 2.0 mg [^] Lactation: 2.6 mg [^]	Low levels associated with IBD (in hair) In DSS-colitis Mn-deficient mice ↑Morbidity, weight loss, colon injury, inflammatory cytokines, oxidative and DNA damage; intestinal permeability Sex-specific differences in mice (Male vs Female) Bacteroidetes: ↓Male ↑Female Verrucomicrobia: ↓Male ↑Female Firmicutes: ↓Male ↑Female ↓M↑F: bacterial genes: phenylalanine synthesis, endotoxin biogenesis, oxidative stress/DNA	Deficient and excess status linked to IR, glucose intolerance, increased T2DM risk Mn supplementation ↑insulin production ↑antioxidant activity ↓pancreatic oxidative stress, renal lipid peroxidation and HTN

RDA values based on adults aged 19–50 years old.

[^]Adequate intake (AI) values are given for Cr and Mn.

control and risk of T2D (Yin *et al.* 2019). In addition, copper-carrying proteins, such as ceruloplasmin, positively correlate with insulin resistance in subjects at increased diabetes risk (Aguilar *et al.* 2013). Lifestyle modifications such as caloric restriction and physical exercise are associated with lower circulating levels of copper bound to ceruloplasmin in people that are overweight (Piacenza *et al.* 2015). Overall, these results show a correlation between higher circulating copper levels and worse blood glucose control. However, the mechanisms of copper's action in animal and *in vitro* models have not clearly defined how this micronutrient influences blood glucose, which may involve pancreatic beta-cell dysfunction and/or peripheral insulin action (Miller *et al.* 1998, Sitasawad *et al.* 2001, Ward *et al.* 2008, Seal & Dey 2018).

Increased circulating copper levels are associated with inflammatory conditions including inflammatory bowel disease (IBD), which may reveal some mechanisms relevant to the influence of copper on the connection

between obesity-inflammation-microbiota and blood glucose control (Stochel-Gaudyn *et al.* 2019) (Fig. 2). Copper deficient diets can negatively impact the intestinal barrier by reducing the expression of ileal tight junction proteins like CLAUDIN-1 and OCCLUDIN (Song *et al.* 2018). Dietary copper alters the abundance of over 20 metabolites including fatty acids (eladic acid, stearic acid, pentadecylic acid) and amino acids (L-threonine, L-aspartic acid, L-proline) in the feces of rats (Wei *et al.* 2015). Dietary copper also alters the abundance of Firmicutes and Verrucomicrobia at the phylum level; *Lactobacillaceae*, *Eubacteriaceae*, *Ruminococcaceae*, *Erysipelotrichaceae*, and *Verrucomicrobiaceae* at the family level, and *Lactobacillus*, *Coprococcus*, *Oscillospira*, *Allobaculum*, and *Akkermansia* at the genus level (Song *et al.* 2018). Elevated copper exposure in pufferfish alters the composition of the gut microbiota which correlates with higher hepatic expression of lipogenic genes and higher liver lipid content (Wang *et al.* 2019a) (Fig. 2). Altogether, these data suggest that dietary

Table 3 The effects of transition metal trace elements on the gut microbiome and host metabolism.

Trace element	Recommended dietary allowance (RDA)	Effects on gut microbiome	Effect on metabolism
Molybdenum (Mo)	Male: 45 µg Female: 45 µg Pregnant: 50 µg Lactation: 50 µg	High supplementation (100 mg/kg) in laying hens ↓Firmicutes ↑Proteobacteria ↑Deltaproteobacteria, Mycococcales, <i>Nanocystaceae</i> ↑circulating ALT, AST Acts as a bacterial cofactor Dehydroxylation by <i>E. lenta</i> in Levodopa metabolism Promotes metabolism and overgrowth of <i>E. coli</i> in DSS-colitis murine model	Positive correlation with T2DM, IR, FBG, glucose intolerance in humans ↓Mo associated with NAFLD risk in humans Mo supplementation ↑glucose tolerance, glycemia in ob/ob mice Prevents hepatic lipid accumulation and oxidative stress
Zinc (Zn)	Male: 11 mg Female: 8 mg Pregnant: 11 mg Lactation: 12 mg	Decreased Zn associated with IBD Zn status linked to enteric infection Deficiency enhanced <i>Shigella flexneri</i> colonization Supplemented <i>S. typhimurium</i> infected broiler chickens mitigated ↓ <i>Lactobacillus</i> , total bacteria Excess Zn increase susceptibility to <i>C. difficile</i> , ↓α-diversity, <i>Turicibacter</i> , ↑ <i>Enterococcus</i> , <i>Clostridium</i> Excess Zn ↑Pathogenic taxa, intestinal permeability and systemic inflammation Zn deficient Broiler chickens: ↓microbial richness, diversity, ↓Firmicutes ↑Proteobacteria, <i>Enterobacteriaceae</i> ↓pathway expression: mineral absorption, carbohydrate digestion and fermentation ↓SCFA	Zn status negatively correlates with glycated hemoglobin + supplementation improves glycemic control in T2DM Zn supplementation: rodent models Improves glucose tolerance, HOMA-beta, insulin secretion in HF-mice ↓hyperglycemia, IR, glucose intolerance, obesity Mechanistic studies Enhance insulin signaling ↑GLUT4 translocation, glucose uptake ↓gluconeogenic enzymes ↓inhibitors of insulin signaling (i.e. PTEN) ↓NFκB activation, cytokine production

RDA values based on adults aged 19–50 years old.

Figure 1
Chromium supplementation improves blood glucose control and alters gut microbes. Image created with BioRender.com.

copper influences gut microbiota, microbial metabolites, and host metabolism, particularly hepatic lipid content, which may provide a link between this micronutrient, gut bacteria, and blood glucose control.

In some countries, copper is added to livestock feed for its antimicrobial and growth-promoting traits. Administration of copper complexed to chitosan nanoparticles in rats decreased potentially pathogenic cecal bacteria (*Salmonella*, *Clostridium*) while increasing the abundance of bacteria with probiotic potential within the genus *Lactobacillus*, which did not occur in rats given copper sulfate (Han *et al.* 2010). Similarly, *Bacillus subtilis* bound to copper administered orally to pregnant and lactating rats enhanced the offspring's survival rate, body weight gain, and development of duodenal villi compared to rats given copper sulfate. These results were associated with reduced intestinal permeability and increased abundance of cecal *Lachnospiraceae*, *Ruminococcaeae*, and *Intestinibacter* (Liu *et al.* 2019a). Although copper supplementation decreased colonic *Streptococci* spp. in piglets, delivery of copper sulfate with and without a microencapsulated protective

Figure 2

High dietary copper ingestion promotes dysbiosis, intestinal inflammation, and a compromised intestinal barrier contributing to poor glucose control. Image created with BioRender.com.

matrix had different effects on the gut microbiota. Animals given encapsulated copper had reduced total bacteria and *Enterobacteriaceae* bacterial cecal counts compared to those receiving unprotected copper (Di Giancamillo *et al.* 2018). In sum, these findings demonstrate different sources of dietary copper and vehicles used to deliver copper can exert unique effects on the gut microbiota.

High dietary copper resulted in the reduction of several *Clostridia* genera and butyrate-producing bacteria such as *Roseburia*, *Acidaminococcus*, and *Coproccoccus*, and increased *Fibrobacteres*, which was associated with changes in protein biosynthesis, gluconeogenesis, amino acid metabolism, galactose metabolism, and protein and carbohydrate metabolites in piglets (Zhang *et al.* 2019). Copper can also decrease SCFA-producing bacteria, and *Lactobacillus*, *Bacillus*, and *Akkermansia*, and increase the abundance of pathogens like *Pseudomonas* and *Acinetobacter* in carp exposed to different doses of this micronutrient. Higher copper exposure was associated with reduced growth indices and expression of intestinal tight junction proteins (Meng *et al.* 2018). Finally, excess dietary copper in mice reduced the abundance of bacteria genera *Staphylococcus*, *Rikenella*, and *Jeotgailcoccus*, but increased the relative abundance of *Corynebacterium*, which was associated with pathological intestinal lesions (Ruan *et al.* 2019). Overall, these results highlight that dietary copper can alter gut microbiota, inflammation, and barrier function that may set up for metabolic inflammation and poor blood glucose control.

Fluoride

Fluoride is added to tap water in most community water systems and dental hygiene products (Whitford 1994). The effect of fluoride on glucose homeostasis is dose-dependent. Fluoride supplementation can increase insulin sensitivity, which may involve the regulation of hepatic glucose transporters (Lobo *et al.* 2015). Fluoride supplementation can also lower hepatic phosphoenolpyruvate carboxykinase (PEPCK), which is

involved in gluconeogenesis (Trevizol *et al.* 2020). Despite these metabolic improvements with supplementation, high fluoride exposure can impair insulin signaling by reducing IRS-1/IRS-2 tyrosine phosphorylation while increasing serine phosphorylation in insulin-responsive tissue, promoting insulin resistance (Chiba *et al.* 2012).

Epidemiological studies suggest that fluoride exposure may be linked with gut inflammation and IBD (reviewed Follin-Arbelet & Moum 2016), but few studies have examined the link between fluoride exposure and gut microbiota. Laying hens exposed to high fluoride (1200 mg/kg) had lower cecal SCFA concentration, impaired intestinal barrier function, and substantial changes to the gut microbiota including (1) higher relative abundance of enteric poultry pathogens like *Chloroflexi*, *Streptococcaceae*, *Gammaproteobacteria*, *Enterobacter*, and *Escherichia shigella*; (2) increased *Proteobacteria*, *Acidobacteria*, *Chloroflexi*, and *Actinobacteria* at the phylum level and (3) enhanced abundance of *Alphaproteobacteria*, *Betaproteobacteria*, *Ktedonobacteria*, and *Gammaproteobacteria* at the class level (Miao *et al.* 2020). In mice, fluoride added to water increased the relative abundance of *Bacteroidetes* and *Actinobacteria* and decreased *Firmicutes*. These fluoride-induced microbial changes were associated with histological gut abnormalities including evidence of a damaged epithelial barrier, decreased crypt depth, and lower epithelial cell proliferation, relative densities of goblet cells, glycoproteins, and intestinal mast cells (Liu *et al.* 2019b). However, one study in mice found no significant shifts in gut microbial community composition with a lower dose and shorter duration of fluoride added to water (Yasuda *et al.* 2017). Therefore, fluoride can alter the intestinal microbiota and gut health in ways that may influence blood glucose, but the dose and duration of fluoride are key factors to consider.

Iodine

Iodine is an essential micronutrient involved in thyroid hormone synthesis. Thyroid hormone is critical to

growth and development, along with multiple metabolic processes including lipid, protein, carbohydrate, vitamin, and mineral metabolism (reviewed in [Mehri 2020](#)). Iodine is generally obtained through the consumption of fish, seafood, dairy, and iodized salt ([National Institutes of Health 2020b](#)). The role of iodine in glucose homeostasis is primarily linked to thyroid hormone production and function. Both hyperthyroid and hypothyroid conditions are linked to insulin resistance ([Maratou *et al.* 2009, 2010](#)). Both iodine deficiency and excess are associated with increased risk of T2D ([Mancini *et al.* 2019, Karakaya *et al.* 2020](#)). In thyroidectomized rats, lower circulating thyroid hormone promotes glucose intolerance, which was mitigated with iodine-containing hormone thyroxine treatment ([Samadi *et al.* 2017](#)). However, higher doses of iodine result in pancreatic toxicity destruction of insulin-secreting beta cells, and hyperglycemia ([Sarkar *et al.* 2018](#)). Excess iodine exposure may impair pancreatic beta-cell insulin secretion and promote apoptosis through the activation of endoplasmic reticulum stress and induction of pro-apoptotic proteins ([Sun *et al.* 2017](#)). Overall, these studies demonstrate that both deficiency or excess iodine is associated with glucose intolerance primarily through effects on thyroid hormones and pancreatic insulin secretion.

Excess iodine in mice can increase adiposity, body weight, and liver weight, with variability in circulating thyroid hormones, including decreased total T4 and thyroid-stimulating hormone and increased free T3 and T4 ([Shen *et al.* 2019](#)). However, obesity may influence the effects of iodine supplementation. Excess iodine in obese high-fat diet mice resulted in weight loss, reduced adiposity and liver weight, and increased circulating thyroid hormone concentrations. Oral iodine supplementation altered the gut flora in obese high-fat fed and lean mice ([Shen *et al.* 2019](#)). Iodine supplementation increased the relative abundance of *Oscillibacter* and *Allobaculum* and decreased *Blautia* in both lean and obese mice. However, some effects of iodine were specific to the gut microbiota of obese mice, where iodine increased the relative abundance of *Enterococcus*, *Clostridium*, and *Fusobacterium nucleatum*, and pathogenic bacteria such as Burkholderiales and *Helicobacter*. Iodine supplementation decreased *Faecalibacterium prausnitzii*, *Lactobacillus*, and *Bifidobacterium* in high-fat fed mice. These findings demonstrate that iodine supplementation can alter host metabolism and the composition of the gut microbiome, where obesity or dietary lipids influence the effect of iodine ([Shen *et al.* 2019](#)).

Manganese

Whole grains, nuts, legumes, and leafy vegetables contain manganese. As a cofactor, manganese participates in processes involved in blood glucose regulation, blood coagulation and hemostasis, and bone growth ([Horning *et al.* 2015](#)). Manganese is also involved in antioxidant production and can participate in responses that lower oxidative stress related to elevated blood glucose and lipids ([Horning *et al.* 2015](#)). Manganese deficiency and excess are both linked to insulin resistance, impaired glucose tolerance, and increased risk of T2D, which may occur in a sex-dependent manner ([Shan *et al.* 2016, Yang *et al.* 2020a](#)). Higher urinary manganese has a linear relationship with HbA1c and fasting blood glucose in women, but urinary manganese has a J-shaped dose-response relationship with insulin resistance and blood insulin in men ([Yang *et al.* 2020a](#)). In addition, high manganese blood levels were reported in obese children ([Fan *et al.* 2017](#)). Blood glucose may influence how manganese is processed since urinary levels may be higher in diabetic patients due to higher excretion, despite a reduction in blood and scalp-hair samples compared to nondiabetic controls ([Kazi *et al.* 2008](#)). Retention of dietary manganese may explain why dietary intake and urinary levels of magnesium have the opposite relationship to blood glucose. In fact, higher dietary manganese intake in postmenopausal women is associated with lower diabetes risk, which may also involve factors such as age and/or hormonal status ([Gong *et al.* 2020](#)). Manganese supplementation can increase insulin secretion and lower blood glucose in diet-induced obese mice ([Lee *et al.* 2013](#)). The ability of manganese to increase insulin secretion is linked to manganese superoxide dismutase (MnSOD) and decreased pancreatic oxidative stress, including lipid peroxidation ([Lee *et al.* 2013](#)). Synthetic delivery of manganese can also suppress lipid peroxidation in kidneys and downregulate the expression of genes known to promote diabetic complications such as nephropathy ([Khan *et al.* 2009](#)). Although supplementation can lower oxidative stress in multiple tissue sites, manganese can also increase pancreatic islet amyloid formation, which can inhibit glucose-stimulated insulin secretion *in vitro* ([Mirhashemi & Shahabaddin 2011, Beck *et al.* 2019](#)). Overall, there is evidence that manganese can promote antioxidant responses that lower blood glucose, but correlations of blood or urinary levels of manganese to blood glucose levels should consider retention and excretion of this micronutrient.

Along with iron and selenium, low levels of manganese determined by hair analyses are associated with newly

diagnosed IBD suggesting insufficiency in these trace elements are correlated with intestinal inflammation (Choi & Yang 2018). In mice, manganese promotes the integrity of the intestinal barrier independent of alterations in the gut microbial profile (Choi *et al.* 2020). Manganese deficiency promotes increased morbidity, weight loss, and colon injury associated with increased inflammatory cytokine levels and oxidative/DNA damage during dextran sulfate sodium (DSS)-induced colitis in mice (Choi *et al.* 2020). High manganese exposure in male rats lowered gut bacterial richness, β -hydroxybutyric acid, and urocanic acid while increasing tryptamine and taurodeoxycholic acid. Fecal microbial transfer from healthy donors to manganese exposed rats increased bacterial diversity and mitigated manganese-induced neurotoxicity and apoptosis (Wang *et al.* 2020). Dietary manganese can lower the alpha diversity of the gut microbiome in both male and female mice, but sex may modify how manganese alters other aspects of the gut microbiota (Fig. 3). Female mice exposed to manganese had higher Bacteroidetes and Verrucomicrobia and lower

Firmicutes, while male mice had lower Bacteroidetes and Verrucomicrobia and higher Firmicutes. Manganese exposure was associated with higher markers of tryptophan and phenylalanine synthesis in the gut microbiota of female mice, but phenylalanine synthesis was lower in male mice exposed to manganese. In addition, gut bacterial genes involved in endotoxin biogenesis, including Kdo2-lipid A synthesis and LPS assembly were decreased in the microbiota of male mice exposed to manganese, which coincided with lower markers of oxidative stress and DNA repair in manganese exposed male mice. However, these manganese-related effects on bacterial endotoxin and host oxidative stress were increased in female mice (Fig. 3). Bacterial genes involved in manganese transport and oxidation were increased in female mice but decreased in male mice (Chi *et al.* 2017). These results suggest that there is a connection between manganese and the host-microbe symbiosis, where sex-specific effects should be considered. It is not yet clear how manganese affects blood glucose via the gut microbiota, but its actions on gut barrier function, inflammation, and oxidative damage could relay signals that alter blood insulin or glucose.

Figure 3

Sex-dependent changes to the gut microbiota are induced by dietary manganese, which may enhance pancreatic insulin secretion and blood glucose regulation. Image created with BioRender.com.

Molybdenum

Molybdenum mainly acts as an enzymatic cofactor (reviewed in Mehri 2020) and is found in various foods including legumes, whole grains, leafy vegetables, dairy products, eggs, and beef (National Institutes of Health 2020c). Urine molybdenum levels positively correlate with insulin resistance and diabetes status (Menke *et al.* 2016). However, its mechanisms of action on blood glucose are not clear. Molybdenum supplementation can lower circulating blood glucose and improve glucose tolerance, without increasing insulinemia in insulin-resistant mice (Reul *et al.* 1997). These results suggest that correlations showing higher molybdenum levels and higher blood glucose do not correspond with mechanistic molybdenum supplementation demonstrating improvements in blood glucose. This discrepancy suggests that the dose of molybdenum and/or excretion/retention of molybdenum are important considerations in the link between this micronutrient and blood glucose. Further, the tissue affected by molybdenum should be considered in any facet of metabolic disease and blood glucose control. Lower circulating concentrations of molybdenum have been associated with increased fatty liver disease (Li *et al.* 2020), while supplementation can lower hepatic lipids, steatosis, and hepatic oxidative stress in mouse models of fatty liver disease (Lee *et al.* 2018).

A high dose of molybdenum (100 mg/kg) lowers the relative abundance of Firmicutes and increases Proteobacteria, Deltaproteobacteria (class), Myxococcales (order), and *Nanocystaceae* (family) in hens. This altered gut profile induced by molybdenum was associated with lower serum antioxidant measures and increased circulating markers of impaired liver function (alanine transaminase (ALT) and aspartate aminotransferase (AST) (Wang *et al.* 2019b). These results suggest the changes in gut microbes correlate with molybdenum-induced effects on liver function.

Molybdenum can also act as a cofactor contributing to gut bacterial enzymatic activity and metabolism. *Eggerthella lenta* is an enteric bacterial species implicated in drug metabolism. This species requires molybdenum for dopamine dehydroxylation, which metabolizes the medication Levodopa used in Parkinson's disease, preventing dopamine from crossing the blood-brain barrier (Maini Rekdal *et al.* 2019). Microbial molybdenum-cofactor-dependent nitrate respiration and formate dehydrogenation may limit the growth of infectious *Enterobacteriaceae*, such as *Escherichia coli*, in inflammation-associated dysbiosis during a murine model of DSS-colitis (Fig. 4). These enzymes require molybdenum to enable metabolic processes critical for pathogenic bacteria to thrive during inflammation (Fig. 4). Administration of tungsten replaces molybdenum thereby inhibiting the molybdopterin cofactor responsible for mitigating *E. coli* growth. These results demonstrate that molybdenum is an important cofactor in bacterial physiology that can be targeted therapeutically to manipulate the gut microbiota during inflammation-induced dysbiosis (Zhu *et al.* 2018).

Selenium

Rich food sources of selenium include seafoods, organ meats, and Pará nuts (National Institutes of Health 2020d). As a selenoprotein, this trace element is involved mainly in antioxidant defenses and in regulating thyroid

function, immunity, and reproduction (reviewed in Mehri 2020). Observational studies demonstrate Vitamins are micronutrients that play a crucial role in the both deficiency and excess of dietary selenium are associated with insulin resistance and increased risk of diabetes (Yadav *et al.* 2017, Lu *et al.* 2019). Multiple randomized controlled trials have tested supplementing selenium in patients with polycystic ovary syndrome, cardiovascular disease, and diabetes, but the effects of supplementation on metabolic parameters such as glucose tolerance, insulin sensitivity, beta-cell function, insulin resistance, and lipid and antioxidant levels are not consistent. However, diabetic coronary heart disease and congestive heart failure patients had lower serum insulin, insulin resistance, circulating LDL cholesterol, C-reactive protein, and higher HDL, and plasma total antioxidant capacity after 8–12 weeks of supplementation with 200 µg/day selenised yeast (Farrokhian *et al.* 2016, Raygan *et al.* 2018). Selenium supplementation increased insulin sensitivity in diabetic nephropathy patients and pregnant women with gestational diabetes (Asemi *et al.* 2015, Bahmani *et al.* 2016). However, selenium supplementation can improve insulin sensitivity some in women with PCOS but promote insulin resistance in other women with PCOS without a clear rationale for the discrepancy (Jamilian *et al.* 2015, Mohammad Hosseinzadeh *et al.* 2016). Overall, these results suggest selenium can improve glucose homeostasis, particularly in patients at risk of diabetes or its complications.

As an antioxidant, selenoproteins can mitigate defects in insulin secretion due to oxidative damage in pancreatic beta cells (Li *et al.* 2015). However, the antioxidant action of selenium can suppress hydrogen-peroxide-mediated insulin signaling (McClung *et al.* 2004). The hepatokine selenoprotein P facilitates selenium transport in blood, has antioxidant properties, and its circulating levels positively correlate with insulin resistance (Misu *et al.* 2010). Administration of neutralizing antibodies targeting selenoprotein P improved insulin secretion and glucose

Figure 4

Molybdenum promotes the growth of potentially pathogenic bacterial and intestinal inflammation, which may lead to aspects of metabolic disease such as poor glucose control. Image created with BioRender.com.

sensitivity in type 2 diabetic mouse models, suggesting targeting this specific selenoprotein may provide therapeutic benefits against T2D (Mita *et al.* 2017).

Circulating levels of selenium are lower in patients with IBD (Stochel-Gaudyn *et al.* 2019); however, it is not yet clear if the role of selenium on gut inflammation is linked to its metabolic effects. Selenium has been used to limit intestinal pathogens in livestock. Culturing cecal microbiota with selenium nanoparticles lowers the abundance of the poultry pathogen *Enterococcus cecorum* (Gangadoo *et al.* 2019). In broiler chickens, organic selenium supplementation increased cecal *Lactobacilli* spp., while suppressing pathogenic *E. coli* and *Salmonella* spp. (Dalia *et al.* 2018) and selenium-enriched yeast increased bacterial diversity and lowered oxidative stress and inflammation (Yang *et al.* 2020b).

Selenium-enriched diets increased gut bacterial diversity in mice, which coincides with the decreased relative abundance of *Parabacteroides*. Mice that harbor microbiota have higher selenium requirements compared to germ-free mice suggesting gut microbes use, biotransform, and compete for selenium with the host (Kasaikina *et al.* 2011). In addition, gut microbes can regulate selenium through the biotransformation from inorganic to organic states to enhance its bioavailability, as well as methylate excess selenium for excretion to prevent toxicity (Krittaphol *et al.* 2011, Zhu *et al.* 2019). Two recent randomized controlled trials examining selenium co-supplementation with a probiotic suggest that combining selenium supplementation with bacterial-based approaches may potentiate its glucose- and insulin-lowering effects (Raygan *et al.* 2019, Tamtaji *et al.* 2019). Overall, these results demonstrate that a bidirectional relationship between host selenium status and the gut microbiota, which regulates the impact of selenium on host glucose metabolism.

Zinc

Zinc is an essential mineral found in red meat, poultry, and oysters (National Institutes of Health 2020e). It is involved in many cellular processes including cell division, protein, and DNA synthesis, wound healing, immune function, and is required for the catalytic activity of various enzymes (Mehri 2020). Generally, zinc intake is inversely correlated with T2D risk. A systematic review analyzing 15 original research studies demonstrates that higher zinc status is correlated with lower HbA1C and that zinc supplementation improved glycemic control in type 2

diabetic patients (de Carvalho *et al.* 2017). Experiments in rodents demonstrate zinc supplementation improves blood glucose tolerance, insulin secretion indices, and glucose-stimulated insulin secretion in diet-induced obese mice (Cooper-Capetini *et al.* 2017). Zinc supplementation also lowers insulin resistance, glucose intolerance, and obesity also in obese KKA(y) mice (Adachi *et al.* 2006). Mechanistically, studies reveal zinc plays a fundamental role in insulin biosynthesis, crystallization, and maturation (Ruz *et al.* 2019). Zinc also exerts insulin-mimetic properties to enhance insulin signaling stimulating GLUT4 translocation and glucose uptake, and by inhibiting the expression of FOXO transcription factors, gluconeogenic enzymes (phosphoenolpyruvate, glucose-6-phosphatase), and negative regulators of PI3K/Akt signaling like phosphatase and tensin homolog protein (PTEN) (Cameron *et al.* 2010, Plum *et al.* 2014, Wu *et al.* 2016). Zinc treatment can also suppress NF κ B activation and subsequent cytokine production in immune cells, demonstrating its anti-inflammatory properties (von Bülow *et al.* 2007). Overall, these studies demonstrate an important role for zinc in regulating blood glucose.

Paneth cells located in the small intestine require zinc import to secrete functional antimicrobial granules with bactericidal activity against infectious agents (Podany *et al.* 2016). Decreased zinc levels are associated with gut inflammatory conditions like IBD (Stochel-Gaudyn *et al.* 2019). Zinc deficiency enhanced the colonization and bacterial persistence of the pathogen *Shigella flexneri* in mice, while supplementation promoted resolution of the pathogen-induced inflammation (Q S Medeiros *et al.* 2019). Zinc supplementation in *Salmonella typhimurium* exposed broiler chickens reversed markers of ileal apoptosis, impairments in intestinal structure, and increased number of cecal *Lactobacillus* and total commensal bacteria during infection (Shao *et al.* 2014). Zinc supplementation may also protect against sepsis by modulating protective immune responses and the gut microbiome, which is reviewed elsewhere (Souffriau & Libert 2018). It is unclear whether zinc and/or zinc-induced antimicrobial peptide production by Paneth cells provide protection against these pathogens in supplemented states. While supplementation may limit some pathogens, excess zinc can promote *Clostridium difficile* susceptibility and toxin activity in mice, which is associated with lower α -diversity, loss of *Turicibacter* genera, and bloom in *Enterococcus* and *Clostridium* genera (Zackular *et al.* 2016). Excess zinc exposure in neonatal mice is also associated with greater expression

of bacterial stress response genes, presence of pathogenic *Pseudomonadales* and *Campylobacter*, increased intestinal permeability, and systemic inflammation (Podany *et al.* 2019). Altogether, these results demonstrate that dietary zinc can influence enteric infections, which may set up for gut inflammation and changes in host metabolism. Zinc-induced changes in blood glucose through changes in commensal bacteria are less clear. One consideration is whether zinc supplementation uses inorganic or organic forms of zinc (Uniyal *et al.* 2017).

Dietary zinc restriction can increase microbial diversity (Gaulke *et al.* 2018) or have no effect on the composition of the gut microbiome in mice (Zackular *et al.* 2016). In broiler chickens, zinc-deficient diets lower cecal microbial species richness and α -diversity, along with a lower relative abundance of Firmicutes, and increased Proteobacteria and *Enterobacteriaceae*. Zinc deficiency resulted in gut bacterial suppression in the expression of pathways involved in mineral (i.e. zinc) absorption, carbohydrate digestion, and fermentation, subsequently leading to decreased SCFA production (Reed *et al.* 2015). Changes in the gut microbiota due to zinc deficiency correlate with increased intestinal permeability in pregnant mice (Sauer & Grabrucker 2019). In human Crohn's disease patients, zinc supplementation improved gut barrier function (Sturniolo *et al.* 2001). Overall, these results demonstrate that dietary zinc deficiency can impair the intestinal barrier, alter gut microbiome processing of carbohydrates, and lower SCFAs production, which may be ways that zinc could influence blood glucose.

Micronutrients: vitamins, gut microbes, and glucose metabolism

Vitamins are micronutrients that play a crucial role in the homeostasis of eukaryotic and prokaryotic cells. These micronutrients are well-positioned to drive selective pressure in the gut bacterial community and influence aspects of host glucose metabolism. Furthermore, while gut microbes can produce vitamin K, B1 (thiamin), B9 (folic acid), and B12 (cobalamin), they can utilize dietary vitamins and affect their availability to the host. Given their prominent role in glucose homeostasis, in the present review, we examine the role of vitamin A, biotin, and thiamin in blood glucose control and discuss the putative implication of gut commensals. A summary outlining the effects of vitamins on gut bacteria and host metabolism is in Table 4.

Vitamin A

Vitamin A is an umbrella term that encompasses different types of lipophilic retinoids, such as retinal, retinol, and retinyl esters. Retinoids are known for being essential for vision, maintenance of epithelial integrity, immunological fitness, and reproduction (Coates *et al.* 2010). Retinoic acid, an oxidized form of Vitamin A, is a key regulator of cell proliferation/differentiation and is essential for the normal growth and development of nearly all tissues in the body (Coates *et al.* 2010). For this reason, an adequate supply of the dietary precursors of retinoic acid is essential throughout the life span, from early in embryonic development to old age. The liver is the most important site for the storage of retinoic acid precursors in the form of retinyl esters and retinol, which can provide substrates for retinoic acid synthesis for long periods of time without the necessity of daily vitamin A intake. Dietary vitamin A can be obtained as preformed vitamin A (retinol and its esterified form, retinyl ester) and provitamin A (carotenoids). After absorption in the small intestine, both forms undergo intracellular enzymatic transformation to yield several metabolites, of which 11-*cis*-retinaldehyde and all-*trans*-retinoic acid (here referred to as retinoic acid) are the major active forms. While the former is critical to normal eyesight function, the latter binds to the nuclear receptor retinoic acid receptor (RAR), which, after dimerization with retinoid X receptor (RXR), binds to retinoic acid-responsive elements (RARE) and regulates several transcriptional programs in various tissues (Coates *et al.* 2010).

Studies using pre-clinical animal models of vitamin A deficiency demonstrate the role of retinoic acid in glucose homeostasis. Lecithin acyltransferase null mice that have a very low storage capacity of retinoids have lower pancreatic β -cell mass insulin secretion defects and blood glucose intolerance when fed a diet low in vitamin A. These metabolic defects were corrected with the reintroduction of vitamin A back into the diet (Trasino *et al.* 2015a). There are several pieces of evidence from pre-clinical obesity models and *in vitro* analysis suggesting that vitamin A supplementation can improve insulin sensitivity (Bonet *et al.* 2012). However, vitamin A supplementation appears to alter insulin sensitivity indirectly through lower visceral fat mass accumulation, which has been mechanistically linked to the enhanced thermogenic programs in white and brown adipocytes and higher fat oxidation (Bonet *et al.* 2012). The role of vitamin A supplementation as an insulin sensitizer acting independently of changes in fat mass warrants further clarification.

Table 4 The effects of vitamins on the gut microbiome and host metabolism.

Vitamin	Recommended dietary allowance (RDA)	Effects on gut microbiome	Effects on metabolism
Vitamin A	Male: 900 µg *RAE Female: 700 µg *RAE Pregnant: 770 µg *RAE Lactation: 1300 µg *RAE	Clostridiales → Retinoic acid → IL-22 → Antimicrobial responses in intestinal epithelial cells Dysbiosis → ↑Proteobacteria → ↓Retinoic acid → ↑ <i>S. typhimurium</i> colonization Germ Free vs Conventional Mice: Retinol/retinoic acid: ↑small intestine, ↓liver Deficiency: promotes Dysbiosis → ↓butyrate producers (genera <i>Clostridium</i> + <i>Roseburia</i>) → gut inflammation + damage gut barrier integrity → impairs insulin sensitivity and blood glucose regulation	Deficiency: glucose intolerance suboptimal insulin response, ↑beta cell apoptosis ↓beta cell mass Supplementation: ↑insulin sensitivity, ↓visceral adiposity Obese mice: ↓retinol in tissues vs lean ↑Retinol binding protein (RBP1) in T2DM and obesity Required for optimal insulin secretion Low circulating levels and lack of transporter associated with diabetes Supplementation: improves glucose tolerance, ↓fasting blood glucose Cofactor for mammalian carboxylases Pharmacological doses lower blood glucose Deficiency: lowers glucose utilization and lipogenesis
Thiamin (Vit. B1)	Male: 1.2 mg Female: 1.1 mg Pregnant: 1.4 mg Lactation: 1.4 mg	Produced by colonic bacteria, like <i>Bacteriodes</i> <i>Enterobacteriaceae</i> negative association to fecal thiamin, associated with hyperglycemia independent of obesity	
Biotin (Vit. B7)	Male: 30 µg^ Female: 30 µg^ Pregnant: 30 µg^ Lactation: 35 µg^	Vancomycin+Biotin Deprivation → Dybiosis → Alopecia Higher intake → Specific Taxonomic features → Correlate with lower visceral fat mass	

RDA values based on adults aged 19–50 years old.

*Vitamin A RDA values are given as retinol activity equivalents (RAE) to account for bioactivity differences of retinol and provitamin A carotenoids, which are then converted into vitamin A. ^Adequate intake (AI) values are given for Biotin.

In murine models of diet- and genetic-induced obesity, lower levels of retinol was found in various tissues, whereas serum retinol was higher in obese mice compared to lean controls (Trasino *et al.* 2015b). This suggests vitamin A deficiency may be associated with defective tissue uptake/delivery and can occur regardless of adequate dietary intake of vitamin A during obesity. Indeed, higher retinol-binding protein (RBP1) has been observed in humans with T2D and obesity (Mody 2017). How the findings from pre-clinical animal studies and cross-sectional human analysis described above translate into feasible treatment strategies against obesity and insulin resistance require further investigation. A phase 2 double-blind randomized clinical trial to test the effect of the synthetic retinoid fenretinide on insulin resistance is underway (Chojkier 2013).

Glucose homeostasis is governed by immunometabolic processes where innate and adaptive immune responses alter insulin sensitivity and blood glucose (Anhê *et al.* 2020b). The gut barrier is an important component of innate immunity as it selectively segregates environmental antigens from inner body compartments. Gut dysbiosis-

driven perturbations to the gut barrier homeostasis are linked to poor glycemic control and insulin resistance (Winer *et al.* 2017). Retinoic acid is instrumental for multiple innate and adaptive immune responses, including lymphocyte activation/proliferation, T helper (Th) cell differentiation, tissue-specific lymphocyte homing, and the production of specific antibody isotypes (Larange & Cheroutre 2016). Specifically, reduction of intestinal Th17 cells occurs in mice fed a vitamin A-deficient high-fat diet, which correlates to worsened metabolic outcomes such as increased weight gain, glucose intolerance, and insulin resistance (Hong *et al.* 2017). This T cell subset can profoundly influence gut microbes, promoting the expansion of commensal bacteria associated with leanness, as demonstrated in hematopoietic cell adoptive-transfer experiments (Hong *et al.* 2017). These results demonstrate how vitamin A can influence host-microbe interactions. In the gut, retinoic acid influences mucosal immunity, eliciting both regulatory and pro-inflammatory responses depending on its concentration and intestinal infectious context (Erkelens & Mebius 2017) (Fig. 5). Gut commensals,

particularly Clostridiales, can downregulate the synthesis of retinoic acid in intestinal epithelial cells, which lowers IL-22 secretion to ensure resolution of antimicrobial responses clear pathogenic bacteria in the gut (Grizotte-Lake *et al.* 2018). However, during vancomycin-driven gut dysbiosis marked by overexpansion of Proteobacteria, the capacity of gut microbes to relay signals to the host via reduced retinoic acid synthesis is compromised, which promotes colonization by pathogens such as *Salmonella typhimurium* (Grizotte-Lake *et al.* 2018). Gut commensal-related regulation of retinoic acid synthesis may be controlled by specific taxa that grow in response to a particular infection since IL-22 is required to clear certain pathobionts from the intestine (Wang *et al.* 2014). In addition, inhibition of retinoic acid synthesis by Clostridiales in the gut likely does not restrain the availability of retinoic acid to other organs, otherwise, it would drive hyperglycemia, which *per se* would damage the gut barrier integrity and ease colonization by pathogens (Thaiss *et al.* 2018). Indeed, while germ-free mice display a higher retinol/retinoic acid ratio in the small intestine compared to mice that harbor a microbiota, the opposite was observed in the liver (Grizotte-Lake *et al.* 2018). Therefore, the net effect of commensal gut microbes is to favor the storage of hepatic retinol, which facilitates normal glucose metabolism. It is also interesting to note that the dysmetabolism seen in murine vitamin A deficiency models is associated with a substantial reduction in butyrate producers from the genera *Clostridium* and *Roseburia* (Tian *et al.* 2018). Low butyrate production is linked to a more pro-inflammatory milieu in the gut and damaged gut barrier integrity (De Vadder *et al.* 2014), which impairs insulin sensitivity and blood glucose regulation. In addition to more robust human trials testing vitamin A as an insulin sensitizer, an important knowledge gap to be filled is how gut microbes tip the balance of retinoic acid synthesis/storage to ensure adequate enteric antimicrobial response and metabolic control at once.

Biotin

Biotin is classified as a B-complex vitamin also known as vitamin B7. Biotin is positioned to alter glucose metabolism because it acts as a cofactor for five mammalian carboxylases involved in the tricarboxylic acid cycle (TCA) cycle: pyruvate carboxylase, propionyl-CoA carboxylase, methylcrotonyl-CoA carboxylase, and two isoforms of acetyl-CoA carboxylase. Biotin is present in animal-based diets and in vegetables such as cauliflower and spinach. It is most often protein-bound, thus requiring

intestinal hydrolysis prior to absorption. As a water-soluble molecule, biotin cannot freely cross the membrane of enterocytes, and therefore, absorption occurs via the sodium-dependent multivitamin transporter. Biotin absorption takes place in the small intestine and in the proximal colon, which positions biotin to interact with commensals and influence host-microbe relationship that alters metabolism (Said 2004). In accordance, recent large-scale metagenomic analysis has shown that the gut microbiota is linked to both synthesis and degradation of B vitamins (Visconti *et al.* 2019).

Pharmacological doses of biotin can lower blood glucose and mitigate other aspects of metabolic syndrome (Aguilera-Mendez *et al.* 2018). Accordingly, pre-clinical studies suggest that biotin deficiency is linked to lower glucose utilization and lipogenesis in parallel to increased gluconeogenic and fat oxidation programs (Velazquez-Arellano *et al.* 2011). Altogether these studies suggest that an adequate dietary intake of biotin is important to maintain euglycemia, and that biotin supplementation may have a value as an adjuvant in the treatment of T2D. If gut commensals influence host blood glucose by altering biotin availability remains to be elucidated. It is known from murine models that vancomycin-driven dysbiosis, when coupled with biotin deprivation, leads to hair loss (Hayashi *et al.* 2017). The fact that dysbiosis and biotin deprivation, alone, were not sufficient to cause alopecia suggests that the gut microbiota can generate enough biotin to affect host physiology (Fig. 5). In agreement, higher biotin intake requires specific taxonomic features in the fecal microbiota to correlate with lower visceral fat mass (Le Roy *et al.* 2019). These findings suggest that gut commensals may mediate the impact of biotin on host blood glucose control at least in part by influencing the buildup of visceral fat (Fig. 5).

Thiamin

Thiamin, or vitamin B1, was the first B-complex water-soluble vitamin described. This vitamin plays an essential role in cellular growth and development, energy metabolism, and oxidative stress (Coates *et al.* 2010). Thiamin is predominantly obtained from the diet but can be synthesized by gut commensals. Free thiamin crosses the gut barrier through specialized transporters located both at the apical and basolateral sides of enterocytes in the proximal small intestine (Said 2011). Thiamin pyrophosphate is the metabolically active form and acts as a cofactor for enzymes involved in carbohydrate metabolism. Thiamin deficiency is linked to neurological

Figure 5

Gut microbes can influence host vitamin status and metabolic health. Image created with BioRender.com.

and cardiovascular diseases. Low intracellular levels of thiamin lead to apoptosis and oxidative stress, which is a common node in diabetic complications such as retinopathy and nephropathy, and neurological disorders (Page *et al.* 2011).

Thiamin is necessary for optimal insulin secretion by pancreatic β -cells (Rathanaswami & Sundaesan 1991). Indeed, lack of a functional thiamin transporter leads to diabetes in humans (Neufeld *et al.* 2001), whereas reduced plasma thiamin has been found in patients with diabetes (Thornalley *et al.* 2007). In addition to its role in β -cell physiology, thiamin deficiency leads to suboptimal activity of key enzymes in carbohydrate metabolism, which ultimately favors the buildup of glucotoxic intermediates linked to endothelial complications associated with hyperglycemia (Page *et al.* 2011). Since the 1940s thiamin supplementation has been shown to improve glucose tolerance and fasting blood glucose (Kaufman 1940) (Fig. 5). These findings have been corroborated more recently and extended to an important beneficial effect of thiamin supplementation on vascular health and oxidative stress in the context of hyperglycemia (Stirban *et al.* 2006).

The amount of absorbable thiamin is regulated by the microbiota and produced by colonic bacteria (Magnúsdóttir *et al.* 2015). Although dietary thiamin is predominantly absorbed in the small intestine, colonocytes also possess the

functional membrane transporters necessary for thiamin absorption (Said *et al.* 2001). This suggests that gut microbial-derived thiamin in the distal gut is positioned to contribute to host thiamin levels and regulate host metabolism (Fig. 5). A recent study using *Drosophila melanogaster* showed that thiamin derived from the gut microbiota is sufficient and necessary to support host physiology in a low-thiamin environment (Sannino *et al.* 2018). How the gut microbiota affects the pool of active thiamin in the host during obesity or metabolic disease is not yet clear. Certain bacteria, such as *Bacteroides*, can biosynthesize thiamin, whereas others, such as *Alistipes* and *Bacilli*, may rely entirely on cross-feeding and/or dietary thiamin (Costliow & Degnan 2017). Thiamin intake may be used as an important selective advantage by certain bacteria, with potential consequences to the host thiamin load. Furthermore, intestinal dysbiosis may be associated with the selection of bacteria that can only transport thiamin to the detriment of producers, which may contribute to lower thiamin availability to the host. The presence of the *Enterobacteriaceae* member *E. coli* in the fecal microbiota of humans was found to be negatively correlated with fecal thiamin (Visconti *et al.* 2019). Interestingly, certain *Enterobacteriaceae* are linked to higher blood glucose independently of obesity (Thingholm *et al.* 2019, Anhê *et al.* 2020a). Further research is needed to test the hypothesis that members of the *Enterobacteriaceae*

family contribute to lower thiamin – and perhaps other B-vitamins – availability to the host, and whether this could be one of the mechanisms by which these bacteria can deteriorate blood glucose control in the host.

Conclusions

Micronutrients, including trace elements and vitamins, interact with the gut microbiota to influence host glucose metabolism. Micronutrients can alter the composition of the intestinal bacteria and commensal microbes influence micronutrient bioavailability. Differences in the source, duration, and experimental models preclude generalizations on the metabolic effects of supplementation of each micronutrient. In addition, characterizing microbial signatures and microbial function at different sites along the gastrointestinal tract, specifically the small intestine where a majority of nutrients are metabolized, would provide further insight into how micronutrients alter glycemia through host-microbe interactions. However, dietary deficiency or excess of nearly every micronutrient compromised host blood glucose metabolism. There has been a focus on macronutrients and the host-microbe relationship in metabolic disease, where carefully controlled mechanistic studies are revealing the role of fat, carbohydrates, and protein in glucose metabolism. Dietary fiber is a key factor, and we propose that dietary micronutrients should be considered in the host-microbe symbiosis relevant to blood glucose control.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review. Dr Jonathan Schertzer is a Senior Editor of Journal of Endocrinology. Dr Schertzer was not involved in the review or editorial process for this paper, on which he is listed as an author.

Funding

This work was supported by grants to J D S from the Canadian Institutes of Health Research (FDN-154295). J D S holds a Canada Research Chair in Metabolic Inflammation.

Author contribution statement

N G B, F F A and J D S wrote the manuscript. All authors edited the manuscript.

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Received in final form 17 May 2021

Accepted 23 June 2021

Accepted Manuscript published online 24 June 2021